4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 870

[Docket No. FDA-2015-N-3387]

Medical Devices; Cardiovascular Devices; Classification of the Coronary Vascular Physiologic Simulation Software Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the coronary vascular physiologic simulation software device into class II (special controls). The special controls that will apply to the device are identified in this order and will be part of the codified language for the coronary vascular physiologic simulation software device's classification. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The classification was applicable on November 26, 2014.

FOR FURTHER INFORMATION CONTACT: Shawn Forrest, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 1326, Silver Spring, MD 20993-0002, 301-796-5554.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a

classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of "low-moderate risk" or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

On November 6, 2013, HeartFlow, Inc. submitted a request for classification of the FFR_{CT} v.1.4 under section 513(f)(2) of the FD&C Act. The manufacturer recommended that the device be classified into class II (Ref. 1).

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1). FDA classifies devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on November 26, 2014, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 870.1415.

Following the effective date of this final classification order, any firm submitting a premarket notification (510(k)) for a coronary vascular physiologic simulation software device will need to comply with the special controls named in this final order.

The device is assigned the generic name coronary vascular physiologic simulation software device, and it is identified as a prescription device that provides simulated functional assessment of blood flow in the coronary vascular system using data extracted from medical device imaging to solve algorithms and yield simulated metrics of physiologic information (e.g., blood flow, coronary flow reserve, fractional flow reserve, myocardial perfusion). A coronary vascular physiologic simulation software device is intended to generate results for use and review by a qualified clinician.

FDA has identified the following risks to health associated with this type of device, as well as the mitigation measures required to mitigate these risks, in table 1.

Table 1.--Coronary Vascular Physiologic Simulation Software Device Risks and Mitigation Measures

Identified Risk	Mitigation Measure
False negative results improperly indicating diseased vessel as low probability for significant disease leads to delay of further evaluation/treatment	Software verification, validation, and hazard analysis Non-clinical performance testing
False positive results improperly indicating diseased vessel as high probability for significant disease leads to incorrect patient management	Clinical testing
Delayed delivery of results leading to delay of further evaluation/treatment	Consistency (repeatability/reproducibility) evaluation Labeling
Failure to properly interpret device results leads to incorrect patient management	Human factors testing Labeling

FDA believes that the following special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness:

- Adequate software verification and validation based on comprehensive hazard analysis with identification of appropriate mitigations, must be performed including:
    - Full characterization of the technical parameters of the software, including any proprietary algorithm(s) used to model the vascular anatomy;
        - Adequate description of the expected impact of all applicable image acquisition hardware features and characteristics on performance and any associated minimum specifications;
    - Adequate consideration of privacy and security issues in the system design; and
        - Adequate mitigation of the impact of failure of any subsystem components (e.g., signal detection and analysis, data storage, system communications and cybersecurity) with respect to incorrect patient reports and operator failures.
- Adequate non-clinical performance testing must be provided to demonstrate the validity of computational modeling methods for flow measurement.
- Clinical data supporting the proposed intended use must be provided, including the following:
    - Output measure(s) must be compared to a clinically acceptable method and must adequately represent the simulated measure(s) the device provides in an accurate and reproducible manner;
    - Clinical utility of the device measurement accuracy must be demonstrated by comparison to that of other available diagnostic tests (e.g., from literature analysis);
    - Statistical performance of the device within clinical risk strata (e.g., age, relevant comorbidities, disease stability) must be reported;

- The dataset must be adequately representative of the intended use population for the device (e.g., patients, range of vessel sizes, imaging device models). Any selection criteria or limitations of the samples must be fully described and justified;
- Statistical methods must consider the predefined endpoints;
  - Estimates of probabilities of incorrect results must be provided for each endpoint;
  - Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification;
  - The report must provide appropriate confidence intervals for each performance metric;
- Sensitivity and specificity must be characterized across the range of available measurements;
- Agreement of the simulated measure(s) with clinically acceptable measure(s) must be assessed across the full range of measurements;
- Comparison of the measurement performance must be provided across the range of intended image acquisition hardware; and
- If the device uses a cutoff threshold or operates across a spectrum of disease, it must be established prior to validation and it must be justified as to how it was determined and clinically validated.

- Adequate validation must be performed and controls implemented to characterize and ensure consistency (i.e., repeatability and reproducibility) of measurement outputs;
  - Acceptable incoming image quality control measures and the resulting image rejection rate for the clinical data must be specified;

- Data must be provided within the clinical validation study or using equivalent datasets demonstrating the consistency (i.e., repeatability and reproducibility) of the output that is representative of the range of data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment;
    - Testing must be performed using multiple operators meeting planned qualification criteria and using the procedure that will be implemented in the production use of the device; and
    - The factors (e.g., medical imaging data set, operator) must be identified regarding which were held constant and which were varied during the evaluation, and a description must be provided for the computations and statistical analyses used to evaluate the data.

- Human factors evaluation and validation must be provided to demonstrate adequate performance of the user interface to allow for users to accurately measure intended parameters, particularly where parameter settings that have impact on measurements require significant user intervention.
- Device labeling must be provided that adequately describes the following:
    - The device's intended use, including the type of imaging data used, what the device measures and outputs to the user, whether the measure is qualitative or quantitative, the clinical indications for which it is to be used, and the specific population for which the device use is intended;

- Appropriate warnings specifying the intended patient population, identifying anatomy and image acquisition factors that may impact measurement results, and providing cautionary guidance for interpretation of the provided measurements;
- Key assumptions made in the calculation and determination of simulated measurements;
- The measurement performance of the device for all presented parameters, with appropriate confidence intervals, and the supporting evidence for this performance. Per-vessel clinical performance, including where applicable localized performance according to vessel and segment, must be included as well as a characterization of the measurement error across the expected range of measurement for key parameters based on the clinical data;
- A detailed description of the patients studied in the clinical validation (e.g., age, gender, race or ethnicity, clinical stability, current treatment regimen) as well as procedural details of the clinical study (e.g., scanner representation, calcium scores, use of beta-blockers or nitrates); and
- Where significant human interface is necessary for accurate analysis, adequately detailed description of the analysis procedure using the device and any data features that could affect accuracy of results.

A coronary vascular physiologic simulation software device is not safe for use except under the supervision of a practitioner licensed by law to direct the use of the device. As such, the device is a prescription device and must satisfy prescription labeling requirements (see 21 CFR 801.109, Prescription devices).

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the coronary vascular physiologic simulation software device they intend to market.

II. Environmental Impact, No Significant Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120, and the collections of information in 21 CFR part 801, regarding labeling have been approved under OMB control number 0910-0485.

IV. Reference

The following reference has been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and is available electronically at http://www.regulations.gov.

1. DEN130045: De Novo Request from HeartFlow, Inc., dated November 1, 2013.

List of Subjects in 21 CFR Part 870

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 870 is amended as follows:

PART 870--CARDIOVASCULAR DEVICES

1. The authority citation for 21 CFR part 870 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 870.1415 to subpart B to read as follows:

§ 870.1415 Coronary vascular physiologic simulation software device.

(a) Identification. A coronary vascular physiologic simulation software device is a prescription device that provides simulated functional assessment of blood flow in the coronary vascular system using data extracted from medical device imaging to solve algorithms and yield simulated metrics of physiologic information (e.g., blood flow, coronary flow reserve, fractional flow reserve, myocardial perfusion). A coronary vascular physiologic simulation software device is intended to generate results for use and review by a qualified clinician.

(b) Classification. Class II (special controls). The special controls for this device are:

(1) Adequate software verification and validation based on comprehensive hazard analysis, with identification of appropriate mitigations, must be performed, including:

(i) Full characterization of the technical parameters of the software, including:

(A) Any proprietary algorithm(s) used to model the vascular anatomy; and

(B) Adequate description of the expected impact of all applicable image acquisition hardware features and characteristics on performance and any associated minimum specifications;

(ii) Adequate consideration of privacy and security issues in the system design; and

(iii) Adequate mitigation of the impact of failure of any subsystem components (e.g., signal detection and analysis, data storage, system communications and cybersecurity) with respect to incorrect patient reports and operator failures.

(2) Adequate non-clinical performance testing must be provided to demonstrate the validity of computational modeling methods for flow measurement; and

(3) Clinical data supporting the proposed intended use must be provided, including the following:

(i) Output measure(s) must be compared to a clinically acceptable method and must adequately represent the simulated measure(s) the device provides in an accurate and reproducible manner;

(ii) Clinical utility of the device measurement accuracy must be demonstrated by comparison to that of other available diagnostic tests (e.g., from literature analysis);

(iii) Statistical performance of the device within clinical risk strata (e.g., age, relevant comorbidities, disease stability) must be reported;

(iv) The dataset must be adequately representative of the intended use population for the device (e.g., patients, range of vessel sizes, imaging device models). Any selection criteria or limitations of the samples must be fully described and justified;

(v) Statistical methods must consider the predefined endpoints:

(A) Estimates of probabilities of incorrect results must be provided for each endpoint,

(B) Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification, and

(C) The report must provide appropriate confidence intervals for each performance metric;

(vi) Sensitivity and specificity must be characterized across the range of available measurements;

(vii) Agreement of the simulated measure(s) with clinically acceptable measure(s) must be assessed across the full range of measurements;

(viii) Comparison of the measurement performance must be provided across the range of intended image acquisition hardware; and

(ix) If the device uses a cutoff threshold or operates across a spectrum of disease, it must be established prior to validation, and it must be justified as to how it was determined and clinically validated;

(4) Adequate validation must be performed and controls implemented to characterize and ensure consistency (i.e., repeatability and reproducibility) of measurement outputs:

(i) Acceptable incoming image quality control measures and the resulting image rejection rate for the clinical data must be specified, and

(ii) Data must be provided within the clinical validation study or using equivalent datasets demonstrating the consistency (i.e., repeatability and reproducibility) of the output that is representative of the range of data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment;

(A) Testing must be performed using multiple operators meeting planned qualification criteria and using the procedure that will be implemented in the production use of the device, and

(B) The factors (e.g., medical imaging dataset, operator) must be identified regarding which were held constant and which were varied during the evaluation, and a description must be provided for the computations and statistical analyses used to evaluate the data;

(5) Human factors evaluation and validation must be provided to demonstrate adequate performance of the user interface to allow for users to accurately measure intended parameters, particularly where parameter settings that have impact on measurements require significant user intervention; and

(6) Device labeling must be provided that adequately describes the following:

(i) The device's intended use, including the type of imaging data used, what the device measures and outputs to the user, whether the measure is qualitative or quantitative, the clinical indications for which it is to be used, and the specific population for which the device use is intended;

(ii) Appropriate warnings specifying the intended patient population, identifying anatomy and image acquisition factors that may impact measurement results, and providing cautionary guidance for interpretation of the provided measurements;

(iii) Key assumptions made in the calculation and determination of simulated measurements;

(iv) The measurement performance of the device for all presented parameters, with appropriate confidence intervals, and the supporting evidence for this performance. Per-vessel clinical performance, including where applicable localized performance according to vessel and segment, must be included as well as a characterization of the measurement error across the expected range of measurement for key parameters based on the clinical data;

(v) A detailed description of the patients studied in the clinical validation (e.g., age, gender, race or ethnicity, clinical stability, current treatment regimen) as well as procedural details of the clinical study (e.g., scanner representation, calcium scores, use of beta-blockers or nitrates); and

(vi) Where significant human interface is necessary for accurate analysis, adequately detailed description of the analysis procedure using the device and any data features that could affect accuracy of results.

Dated: October 14, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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